ATENT COOPERATION TR TY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D 2145 PCT/2		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08827	08/09/2000	10/09/1999
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant EPIDAUROS BIOTECHNOLOGIE AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/02/2001	11.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Leber, T Telephone No. +49 89 2399 7195

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08827

I. Basis f the r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-47 as originally filed

Claims, No.:

1-37 as received on 29/11/2001 with letter of 26/11/2001

Drawings, sheets:

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-45, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-29,32-37(partially);30,31(completely).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 22-26 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 30,31(completely);1-29,32-37(partial).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-37(partly).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-8, 10-21, 27-29, 33-37

	No:	Claims	9,32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8, 10-21, 27-29, 33-37
Industrial applicability (IA)	Yes:	Claims	1-21, 27-29, 3-37
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II
Priority

1. Priority was checked with respect to the first and fully searched invention referred to in the present application (see Item IV 1.). Priority was found not to be valid as the priority document does not disclose the molecular variant M20 which shows a nucleotide substitution G-201A.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims relating to inventions in respect of which no International Search Report has been established (claims 30, 31 (completely); claims 1-29, 32-37 (partially)) need not to be the subject of International Preliminary Examination (Rule 66(1)(e) PCT; see PCT/ISA/210, dated 05.06.2001). Accordingly, only those parts which are identified in the International Search Report as having been searched are subject of this International Preliminary Examination. With respect to the sequences referred to in the present invention, the sequences SEQ ID NO: 56, 17, 18, 36 and 37 have been searched as these are considered to relate to the first invention (see PCT/ISA/210, dated 05.06.2001).

2. Claim 22 refers to a method of diagnosing in a sample a disorder related to the molecular variant of the hPXR gene. In view of the non-unity objections raised by the ISA (PCT/ISA/210, dated 05.06.2001) only the first invention has been fully searched (see Item IV). The resulting subject-matter relates to the mutation G-201A which, according to the description of the present application, has no impact on the protein being produced from that molecular variant as the mutation is located in the 5'UTR region of exon 1a (Table 4). Moreover, an impact on gene expression has not been disclosed in the description. Therefore, claim 22 lacks support by the description to such an extent that no meaningful opinion can be formed (Art 34(4)(a)(ii) PCT). The same objection is raised against claims 23-26.

R It m IV

Lack of unity of invention

1. The International Searching Authority considered that 19 inventions are present in the international patent application, contrary to the requirements of Rule 13.1 PCT and invited the Applicant to pay additional searching fees (PCT/ISA/206, dated 19.03.2001). As no further searching fees were paid by the Applicant, the International Search Report (PCT/ISA/210, dated 05.06.2001) was established for the first invention encompassing claims 1-43 (all partially) as originally filed. The said invention relates to the molecular variant M20 (page 41, Table 4) of hPXR showing a mutation at position -201 and the short oligonucleotide (Seq ID 56) useful for the detection of a mutation in exon 1a (Table 5).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Basis for the assessment of novelty, inventive step and industrial applicability

1.1 Reference is made to the following documents:

D1: WO 99 48915 A (GLAXO GROUP LTD ;KLIEWER STEVEN ANTHONY (US); WILLSON TIMOTHY MARK) 30 September 1999 (1999-09-30)

D2: LEHMANN J M ET AL.,: 'The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions.' JOURNAL OF CLINICAL INVESTIGATION, vol. 102, 1 September 1998 (1998-09-01), page 1016-1023 XP000909297 cited in the application

D3: KLIEWER S A ET AL: 'AN ORPHAN NUCLEAR RECEPTOR ACTIVATED BY PREGNANES DEFINES A NOVEL STEROID SIGNALING PATHWAY' CELL,CELL PRESS, CAMBRIDGE, NA,US, vol. 92, 9 January 1998 (1998-01-09), pages 73-82, XP000918927 ISSN: 0092-8674

D4: DOTZLAW H ET AL.,: 'The human organ receptor PXR messenger RNA is

expressed in both normal and neoplastic breast tissue.' CLINICAL CANCER RESEARCH, vol. 5, August 1999 (1999-08), pages 2103-2107, XP000929536

1.2 The amendments filed with letter of 26.11.2001 appear to fulfil the requirements of Art 34(2)(b) PCT.

2. Novelty

2.1 Claim 1 of the present application appears to be novel (Art 33(2) PCT) as none of the documents cited in the ISR disclose the sequence of SEQ ID NO: 56 or a polynucleotide encoding for hPXR whereby position -201 is an A or mutated in any other way. The dependent claims 2 and 3 and the claims encompassing claim 1 (claims 4-8, 12-16, 36, 37) are thus also novel (Art 33(2) PCT).

2.2 As disclosed in the description of the present application, no effect is predicted to be associated with the mutation at position -201 (page 41, Table 4). Therefore, the protein resulting from this gene appears to be identical to that resulting from the wild type gene.

2.3 Claim 9 refers to a product ("hPXR protein or a fragment thereof") being produced by a novel process. A product, however, is not rendered novel merely by the fact that it is produced by a novel process. Thus, in view of the above (Item V, 2.2), claim 9 lacks novelty (Art 33(2) PCT) as the prior art documents disclose the hPXR protein (D2, page 1018, Fig. 1D; D3, page 74, Fig. 1A; D4, page 2104, left column; page 2105 Fig. 2).

2.4 Claims 10 and 11 appear to be novel (Art 33(2) PCT) as none of documents cited in the ISR disclose an antibody to hPXR or a fragment thereof. Claim 35 is thus also novel (Art 33(2) PCT).

2.5 Claim 17 appears to be novel (Art 33(2) PCT) as none of the documents cited in the ISR disclose a competitive assay as proposed in the said claim to determine an inhibitor of hPXR. The dependent claims 18-21, the independent claim 27 and claims 28 and 29 dependent thereon are thus also novel (Art 33(2) PCT; see also

ITEM VIII-5.).

2.6 D2 discloses the use of the ligand binding domain of hPXR, which is located at the C-terminus of the said protein and therefore not influenced by the mutation at position -201 for the detection of hPXR mRNA in different tissues (D2, page 1017, left column, "Northern analysis"; page 1018, Fig. 1B; page 1019 Fig. 2). Thus, claim 32 lacks novelty (Art 33(2) PCT). Similar assays are shown in D3 (D3, page 75, Fig. 2A; page 80 "Northern analysis") and D4 (D4, page 2104, "RNA extraction..."; Fig. 1).

2.7 Claim 33 appears to be novel (Art 33(2) PCT) as none of the sequences SEQ ID NO: 56, 17, 18, 36 and 37 are disclosed in the prior art (see also ITEM V, 1.2). Claim 34 is novel for the same reason (Art 33(2) PCT).

2.8 In conclusion, claims 1-8, 10-21, 27-29, 33-37 appear to be novel over the prior art (Art 33(2) PCT).

3. Inventive step

3.1 Claim 1 refers to a polynucleotide which encodes a hPXR polypeptide. The polynucleotide referred to in claim 1c and d differs from the closest prior art documents D1 (D1, Fig. 1), D2 (D2, Fig. 1A) and D3 (D3, Fig. 1A) in that at position -201 of the hPXR gene at a single nucleotide difference exists. As disclosed in the description of the present application, the mutation G-201A found in African individuals is neither predicted to affect the encoded protein (page 41, Table 4) nor is any information presented showing that said mutations cause an altered expression of the gene. The technical problem is thus to provide an alternative polynucleotide encoding the same hPXR polypeptide. The solution referred to in claim 1 is to provide a polynucleotide which differs from the prior art in a single nucleotide at position -201 in the 5' UTR of the hPXR gene. It appears that this solution lacks an inventive step (Art 33(3) PCT) as it is obvious for the skilled person that mutations in the 5' UTR do not affect the encoded protein. Thus, claim 1 lacks an inventive step (Art 33(3) PCT).

3.2 Claims 2-8, 12-14, 36, 37 appear not to contain features which in combination with

the features of the claims to which they refer fulfill the requirements of Art 33(3) PCT for inventive step.

3.3 Claim 10 refers to an antibody which binds to the protein in claim 9 which is encoded by any of the sequences referred to in claim 1-3. Claim 10 differs from the closest prior art D1-D4 in that it provides an antibody for hPXR. The technical problem is to provide an antibody. For the skilled person it is a routine procedure to develop antibodies to a protein and the required laboratory procedures are standard knowledge. It is also known to the skilled person that instead of the full protein only a small peptide can be used in these procedures. Moreover, it appears, no particular effect is associated with the antibodies referred to in claim 10. Thus, an inventive step can not be acknowledged for claims 10, 11 and 35.

3.4 Claim 15 refers to a method for the detection of an inhibitor capable of modulating the activity of a variant of hPXR. The method involves contacting a variant hPXR with a compound and measuring the activity of downstream mediators CYP3A4 or CYP3A7. Claim 15 differs from the closest prior art document D2 (D2, claim 11) in that the hPXR protein is encoded by a genetic variant which, however, does not influence the amino acid composition of the protein or the level of expression of the gene(see Item V, 2.2 above). The technical problem is thus to provide an alternative polynucleotide encoding the same hPXR polypeptide. The solution referred to in claim 15 is to provide a polynucleotide which differs from the prior art in a single nucleotide at position -201 of the hPXR gene. It appears that this solution lacks an inventive step (Art 33(3) PCT) as it is obvious for the skilled person that mutations in the 5' UTR do not affect the encoded protein.
Claim 16 lacks an inventive step (Art 33(3) PCT) for the same reasons.

3.4 Claim 17 differs from the closest prior art document D2 (D2, claim 11) in that the compound screening method is based on a competitive assay in which the compound to be tested is measured against a known compound which binds to hPXR. The technical problem is to provide an improved method for compound screening. The solution is to employ a competitive assay. It appears that an inventive step (Art 33(3) PCT) can not be acknowledged for said solution as it belongs to the standard knowledge of the skilled person to perform within the search of a suitable, activity modulating compound both, direct

inhibition/enhancing studies as in D1 (D1, claim 11) and competitive assays as proposed in claim 17 of the present application.

3.5 Claims 18-21 and 27-29 appear not to contain features which in combination with the features of the claims to which they refer fulfill the requirements of Art 33(3) PCT.

3.6 Claim 33 refers to oligonucleotides of 15-50 nucleotides for detection of a polynucleotide as referred to in claims 1-3 and/or genotyping of hPXR alleles. In view of the unity objection raised by the ISA (see Item V 1.2 above), claim 33 is limited to oligonucleotides which are related to the nucleotide at position -201 of the hPXR gene and thus to the sequences identified in SEQ ID NO: 56, 17, 18, 36 and 37 of the present application. These sequences are not disclosed in the prior art. The sequence of SEQ ID NO:17 is located within exon 1b and can due to its orientation not be used to, for example, determine whether or not the mutation G-201A is present (Fig. 4 "Exon1a&1b"). This sequence thus represent a random selection of an oligonucleotide from a known sequence (D1, SEQ ID NO:13). A technical problem appears not to be associated with the sequence SEQ ID NO:17. Therefore, an inventive step can not be acknowledged for claim 33 (Art 33(3) PCT). Claim 34 lacks an inventive step for the same reason (Art 33(3) PCT).

4. Industrial applicability

4.1 The subject-matter disclosed in the claims 1-21, 27-29, 32-37 of the present application appears to be industrially applicable (Art 33(4) PCT).

Re Item VI
Certain documents cited

1. The following documents, which have an earlier priority and filing date than the present application, may be of relevance for the examination of the present application in its regional or national phase.

   a: WO 99 48915 A (GLAXO GROUP LTD ;KLIEWER STEVEN ANTHONY

(US); WILLSON TIMOTHY MARK) 30 September 1999 (1999-09-30)

b: EP-A-1 024 193 (CHUGAI PHARMACEUTICAL CO LTD) 2 August 2000 (2000-08-02)

Re Item VII

Certain defects in the international application

1. The expression "herein incorporated by reference" or equivalents thereof (e.g. page 2, first paragraph) in the description of the present application should be deleted (Guidelines, Section IV, II-4.17).

2. To meet the requirements of Art 5 and Rule 5 PCT, the documents D1-D4 should be identified in the description and the relevant background art disclosed therein should be briefly discussed if the subject-matter for which these documents are relevant prior art remains in the claims.

Re Item VIII

Certain observations on the international application

1. Claims should be defined by technical features (Rule 6.3a PCT). A sequence being defined by a database accession numbers only, however, does not fulfil this requirement. In its present form the accession number represents only internal designations which is, as such, unknown to the skilled person. Moreover, the description shall indicate background art which is useful for understanding, searching and examination of the invention (Rule 5.1(a)(ii) PCT). A database accession number does do not follow Rule 13ter for sequence listing. Therefore, search and examination cannot be performed thereon. Moreover, database entries may change over time, thus there appears to be a lack of reproducibility (Art 5 PCT). Finally, claim 1 neither provides information as to which database to be used nor how to access it, resulting in a lack of clarity and reproducibility (Art 5 and 6 PCT).

2. The term "fragment" in claim 2 results in a lack of clarity (Art 6 PCT).

3. Claim 3 suggests that the nucleotide exchange results in an "altered expression" of the hPXR gene. The description, however, provides no information as to whether mutations at position -201 in the 5' UTR affect the expression of hPXR (see Table 4). Thus, claim 3 lacks support by the description (Art 6 PCT).

4. Claim 15 lacks clarity (Art 6 PCT) as the subject-matter of this claim is only defined by the result to be achieved lacking technical features ("... components capable of providing a detectable signal in response to drug metabolisation, with a compound to be screened under conditions..."). Moreover, the meaning of claim 15 is unclear (Art 6 PCT) as the proteins resulting from claims 1-3 are wild-type proteins because the mutations at -201 are located in the 5'UTR of Exon 1a (Table 4) and as Seq ID 56 encodes at best for four amino acids which are unlikely to have a biological activity similar to hPXR. The same objection applies to claim 17. In addition, claim 15 lacks clarity as to whether the "component", "drug" and "compound" refer to the same or different substances (Art 6 PCT). Finally, the description suggests that substances which bind to hPXR result in increase expression of CYP3A as hPXR dimerises with RXR and binds to the rifampicin/dexamethasone response element in the CYP3A4 promoter. It is thus unclear (Art 5 and 6 PCT) how an inhibitor of hPXR can be found if that inhibitor increases CYP3A4 or CYP3A7 drug metabolisation as referred to in claim 15.

5. A clerical error appears to have occurred in claim 28, which in its present from refers to claim 30. In view of the claims as originally filed, it is assumed that this claim was intended to refer to amended claim 27.

6. The term "derivative" in claim 30 lacks clarity and support by the description (Art 6 PCT).

7. Claim 33 appears to be contradictory in itself as, for example, the said oligonucleotide can not be 15 nucleotides long and at the same time comprise the sequence of SEQ ID NO 17, which is already 24 nucleotides long (Art 6 PCT).

8. In view of the subject-matter disclosed in present application, the number of 22 independent claims appears to be excessive resulting in a lack of clarity (Art 6 PCT) and conciseness of the application (Rule 6.1a PCT).

PCT/EP00/08827
Epidauros Biotechnologie GmbH
Our Ref.: D 2145 PCT/2

Claims

1. A polynucleotide selected from the group consisting of:

   (a) a polynucleotide having the nucleic acid sequence of SEQ ID NO: 56, 57, 60, 61, 64, 65, 68, 69, 72, 73, 76, 77, 80, 81, 84, 85, 88, 89, 92, 93, 96, 97, 100, 101, 104, 105, 108, 109, 112, 113, 116, 117, 120, 121, 124, 125, 128, 129, 132, 133, 136, 137, 140, 141, 144, 145, 148, 149, 152, 153, 156, 157, 160, 161, 164, 165, 166, 168, 170, 172, 174 or 176;

   (b) a polynucleotide encoding a polypeptide having the amino acid sequence of SEQ ID NO: 167, 169, 171, 173, 175 or 177;

   (c) a polynucleotide encoding a hPXR polypeptide, wherein said polynucleotide is having at a position corresponding to position –201, -131, -57, -42, 52, 79, 106, 225, 315, 418, 488, 492, 543, 696, 834, 984, 1108, 1308 or 1320 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1), at position corresponding to position –100 or –20 of the hPXR gene (Accession No: gi3769536, wherein the A of the start codon ATG at position 60 has been numbered +1), at a position corresponding to position –29 of Intron 2 of the hPXR gene (Accession No: gi3769538, wherein Exon 3 starts at position 477), at a position corresponding to position +72 of Intron 3 of the hPXR gene (Accession No: gi3769538, wherein Exon 3 ends at position 610), at a position corresponding to position +99 of Intron 6 of the hPXR gene (Accession No: gi3769538, wherein Exon 6 ends at position 1216), at a position corresponding to position -73 or –17 of Intron 6 of the hPXR gene (Accession No: gi3769538, wherein Exon 7 starts at position 1217), at a position corresponding to position +36 of Intron 7 of the hPXR gene (Accession No:

gi3769538, wherein Exon 7 ends at position 1333) or at a position corresponding to position +43 of Intron 8 of the hPXR gene (Accession No: gi3769538, wherein Exon 8 ends at position 1439) a nucleotide exchange, a nucleotide deletion, an additional nucleotide or a nucleotide deletion and a nucleotide exchange;

(d) a polynucleotide encoding a hPXR polypeptide, wherein said polynucleotide is having at a position corresponding to position –201, -131, 52, 106, 418, 834, 1108, 1308 or 1320 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1) or at a position corresponding to position +99 of Intron 6 of the hPXR gene (Accession number: gi3769538, wherein Exon 6 ends at position 1216) or at a position corresponding to position +43 of the Intron 8 of the hPXR gene (Accession number: gi3769538, wherein Exon 8 ends at position 1439) an A, at a position corresponding to position -57, 79, 315, 543, 696 or 984 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1) or at a position corresponding to position –29 of Intron 2 of the hPXR gene (Accession No: gi3769538, wherein Exon 3 starts at position 477), at a position corresponding to position -17 of Intron 6 of the hPXR gene gene (Accession number: gi3769538, wherein Exon 7 starts at position 1217) or at a position corresponding to position +36 of Intron 7 of the hPXR gene gene (Accession number: gi3769538, wherein Exon 7 ends at position 1333) a T, at a position corresponding to position –20 of the hPXR gene (Accession number No: gi3769536, wherein the A at the start codon ATG at position 60 has been numbered +1) a deletion, at position corresponding to position –42, 225 or 492 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation initiation site at position 280 has been numbered +1) a C or at a position corresponding to position 488 of the hPXR gene (Accession No: gi3769538, wherein the C of the CTG translation

initiation site at position 280 has been numbered +1), at a position corresponding to position -100 of the hPXR gene (Accession No: gi3769536, wherein the A of the start codon ATG at position 60 has been numbered +1), at a position corresponding to position +72 of Intron 3 of the hPXR gene (Accession No: gi3769538, wherein Exon 3 ends at position 610) or at a position corresponding to position –73 of Intron 6 of the hPXR gene gene (Accession No: gi3769538, wherein Exon 7 starts at position 1217) a G;

(e) a polynucleotide encoding a hPXR polypeptide, wherein said polypeptide comprises an amino acid substitution at position 18, 27, 36, 140, 163 or 370 of the hPXR polypeptide (Accession No: gi3769538, wherein the C of the start codon CTG is at position 280); and

(f) a polynucleotide encoding a hPXR polypeptide, wherein said polypeptide comprises an amino acid substitution of E to K at position 18, of P to S at position 27, of G to R at position 36, of V to M at position 140, of D to G at position 163 or of A to T at position 370 of the hPXR polypeptide (Accession No: gi3769538).

2. The polynucleotide of claim 1, wherein said polynucleotide encodes a variant hPXR protein or fragment thereof.

3. The polynucleotide of claim 1 or 2, wherein the nucleotide deletion, addition and/or substitution result in altered expression of the hPXR gene compared to the corresponding wild type gene.

4. A vector comprising the polynucleotide of any one of claims 1 to 3.

5. The vector of claim 4, wherein the polynucleotide is operatively linked to expression control sequences allowing expression in prokaryotic or eukaryotic cells.

6. A host cell genetically engineered with the polynucleotide of any one of claims 1 to 3 or the vector of claim 4 or 5.

7. A method for producing a molecular variant hPXR protein or fragment thereof comprising
   (a) culturing the host cell of claim 6; and
   (b) recovering said protein or fragment from the culture.

8. A method for producing cells capable of expressing a molecular variant hPXR gene comprising genetically engineering cells with the polynucleotide of any one of claims 1 to 3 or the vector of claim 4 or 5.

9. A hPXR protein or fragment thereof encoded by the polynucleotide of any one of claims 1 to 3 or obtainable by the method of claim 7 or from cells produced by the method of claim 8.

10. An antibody which binds specifically to the protein of claim 9.

11. The antibody of claim 10 which specifically recognizes an epitope containing one or more amino acid substitution(s) as defined in any one of claims 1 to 3.

12. A transgenic non-human animal comprising at least one polynucleotide of any one of claims 1 to 3 or the vector of claim 4 or 5.

13. The transgenic non-human animal of claim 12 further comprising at least one inactivated wild type allele of the hPXR gene.

14. The transgenic non-human animal of claim 12 or 13, which is a mouse or a rat.

15. A method of identifying and obtaining a hPXR inhibitor capable of modulating the activity of a molecular variant of the hPXR gene or its gene product comprising the steps of

(a) contacting the protein of claim 9 or a cell expressing a molecular variant hPXR gene comprising a polynucleotide of any one of claims 1 to 3 in the presence of components capable of providing a detectable signal in response to drug metabolization, with a compound to be screened under conditions to permit CYP3A4- or CYP3A7-mediated drug metabolization, and

(b) detecting the presence or absence of a signal or increase of a signal generated from the drug metabolization, wherein the presence or increase of the signal is indicative for a putative inhibitor.

16. The method of claim 15 wherein said cell is a cell of claim 6, obtained by the method of claim 8 or is comprised in the transgenic non-human animal of any one of claims 12 to 14.

17. A method of identifying and obtaining an hPXR inhibitor capable of modulating the activity of a molecular variant of the hPXR gene product comprising the steps of

(a) contacting the protein of claim 9 with a first molecule known to be bound by hPXR protein to form a first complex of said protein and said first molecule;

(b) contacting said first complex with a compound to be screened; and

(c) measuring whether said compound displaces said first molecule from said first complex.

18. The method of claim 17, wherein said measuring step comprises measuring the formation of a second complex of said protein and said compound.

19. The method of claim 17 or 18, wherein said measuring step comprises measuring the amount of said first molecule that is not bound to said protein.

20. The method of any one of claim 17 to 19 wherein said first molecule is nifedipine, rifampicine or corticosterone.

21. The method of any one of claims 17 to 20 wherein said first molecule is labeled.

22. A method of diagnosing a disorder related to the presence of a molecular variant of the hPXR gene or susceptibility to such a disorder comprising
(a) determining the presence of a polynucleotide of any one of claim 1 to 3 in a sample from a subject; and/or
(b) determining the presence of a protein of claim 9.

23. The method of claim 22, wherein said disorder is cancer.

24. The method of claim 22 or 23 comprising PCR, ligase chain reaction, restriction digestion, direct sequencing, nucleic acid amplification techniques, hybridization techniques or immunoassays.

25. The method of any one of claims 22 to 24, further comprising administering to a subject a medicament to abolish or alleviate said disorder.

26. The method of any one of claims 22 to 25, further comprising introducing a functional and expressible wild type hPXR gene into cells.

27. A method for the production of a pharmaceutical composition comprising the steps of the method of any one of claims 15 to 21; and
(c) synthesizing and/or formulating the compound identified and obtained in step (b) in a pharmaceutically acceptable form.

28. The method of claim 30, wherein said compound is a drug or prodrug in a form suitable for therapeutic application and preventing or ameliorating the disorder of the subject diagnosed in the method of claim 22 or 23.

29. The method of claim 27 or 28 wherein said compound drug or prodrug is a derivative of a medicament as defined in claim 25.

30. An inhibitor identified or obtainable by the method of any one of claims 15 to 21.

31. The inhibitor of claim 30 which binds specifically to the protein of claim 9.

32. Use of an oligo- or polynucleotide for the detection of a polynucleotide of any one of claims 1 to 3 and/or for genotyping of individual hPXR alleles.

33. The use of claim 32 wherein said oligonucleotide is 15 to 50 nucleotides in length and comprises the nucleotide sequence of any one of SEQ ID NOS: 1 to 165 or a complementary sequence.

34. A primer or probe consisting of an oligonucleotide as defined in claim 33.

35. Use of an antibody for the detection of the protein of claim 9, the expression of a molecular variant hPXR gene comprising a polynucleotide of any one of claims 1 to 3 and/or for distinguishing hPXR alleles comprising a polynucleotide of any one of claims 1 to 3.

36. A composition comprising the polynucleotide of any one of claims 1 to 3, the vector of claim 4 or 5, the host cell of claim 6 or obtained by the method of claim 8, the protein of claim 9, the antibody of claim 10 or 11, the inhibitor of claim 30 or the primer or probe of claim 34.

37. The composition of claim 36 which is a diagnostic or a pharmaceutical composition.